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EXAMINER	
STANTON, B	
ART UNIT	**PAPER NUMBER**
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DATE MAILED: 04/25/96

This is a communication from the examiner in charge of your application.
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For Restriction Purposes only.

☑ This application has been examined Λ ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire ~~0~~ month(s), 30 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 63-79 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☑ Claims 1-62 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☐ Claims _____ are rejected.
5. ☐ Claims _____ are objected to.
6. ☑ Claims 63-79 are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

The amendment filed 2/15/96 (Paper No. 10) has been entered. Previously pending claims 1-62 have been cancelled. Newly advanced claims 63-79 are pending in the instant Application.

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 63 and 64, drawn to methods for treating cytokine mediated toxicity comprising inhibiting MIF gene expression, classified in various classes and subclasses dependent upon the nature of the inhibitor; for example, methods employing antisense nucleic acids are classified in Class 514, subclass 44.

II. Claims 65-67, drawn to methods for treating cytokine mediated toxicity comprising modulating MIF biologic activity, classified in various classes and subclasses dependent upon the nature of the inhibitor; for example, methods employing antibodies are classified in Class 424, subclass 130.1.

Claims 65-67 are generic to a plurality of disclosed patentably distinct species comprising:

a. using anti-MIF-receptor antibodies;
b. using MIF antagonists;

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species, even though this requirement is traversed. Following said election, the claims of the instant invention will only be examined to the extent that they read on the elected species. Claims not directed to said species will be **WITHDRAWN** from consideration.

The species delineated above are distinct, one from the other because they utilize materially different biologic agents each of which requires separate areas of search and consideration. For example, species (a) requires search and consideration of antibodies; and species (b) of altered forms of cellular receptors.

III. Claims 68 and 69, drawn to methods for treating cytokine mediated toxicity comprising inhibiting MIF-receptor gene expression, classified in various classes and subclasses dependent upon the nature of the inhibitor; for example, methods employing antisense nucleic acids are classified in Class 514, subclass 44.

IV. Claims 70 and 71, drawn to methods for treating cytokine mediated toxicity comprising modulating MIF receptor biologic activity, classified in various classes and subclasses dependent upon the nature of the inhibitor; for example, methods employing antibodies are classified in Class 424, subclass 130.1.

Claims 70 and 71 are generic to a plurality of disclosed patentably distinct species comprising:

a. using anti-MIF-receptor antibodies;
b. using MIF antagonists;

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species, even though this requirement is traversed. Following said election, the claims of the instant invention will only be examined to the extent that they read on the elected species. Claims not directed to said species will be **WITHDRAWN** from consideration.

The species delineated above are distinct, one from the other because they utilize materially different biologic agents each of which requires separate areas of search and consideration. For example, species (a) requires search and consideration of antibodies; and species (b) of altered forms of cellular receptors.

V. Claim 72, drawn to MIF receptor proteins, classified in Class 530, subclass 350.

VI. Claims 73 and 74, drawn to methods for treating cytokine mediated toxicity comprising inhibiting MIF release, classified in various classes and subclasses dependent upon the nature of the inhibitor.

VII. Claim 75, drawn to methods of identifying compounds that inhibit MIF release, classified in Class 435, subclass 4.

VIII. Claim 76, drawn to methods of inhibiting the toxic side effects of steroids, classified in various Classes and subclasses dependent upon the agent used.

IX. Claim 76, drawn to methods of enhancing anti-inflammatory activity of steroids, classified in various Classes and subclasses dependent upon the agent used.

Claim 76 is generic to a plurality of disclosed patentably distinct species and subspecies comprising:

a. using agents that inhibit MIF biologic activity;
b. using agents that inhibit MIF receptor biologic activity;
c. using agents that inhibit MIF gene expression;
d. using agents that inhibit MIF receptor gene expression;
e. using agents that inhibit MIF release;

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species, even though this requirement is traversed. Following said election, the claims of the instant invention will only be examined to the extent that they read on the elected species. Claims not directed to said species will be **WITHDRAWN** from consideration.

In regard to each species (a)-(e) above, each particular mechanism of inhibiting MIF biologic activity is distinct from the other because they proceed via materially different processes that require separate areas of search and consideration. For example, species (a) and (b) requires search and

consideration of the biological activity of distinct proteins (MIF or MIF receptor); species (c) and (d) require search and consideration of the alteration of gene expression of separate genes (those encoding MIF or MIF receptor, respectively); and species (e) requires search and consideration of cellular and molecular control of MIF release.

X. Claim 77, drawn to combination therapies for treatment of cytokine mediated toxicity, classified in various Classes and subclasses dependent upon the agent used.

Claim 77 is generic to a plurality of disclosed patentably distinct species and subspecies comprising:

A. Agent (a):

a. using agents that inhibit MIF biologic activity;
b. using agents that inhibit MIF receptor biologic activity;
c. using agents that inhibit MIF gene expression;
d. using agents that inhibit MIF receptor gene expression;
e. using agents that inhibit MIF release;

B. Agent (b):

a. using anti-TNFα;
b. using anti-IL-1;
c. using anti-IFN-γ;
d. using IL-1RA;
e. using a steroid;
f. using a glucocorticoid;
g. using IL-10;

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species, even though this requirement is traversed. Following said election, the claims of the instant invention will only be examined to the extent that they read on the elected species. Claims not directed to said species will be **WITHDRAWN** from consideration.

In regard to species (A)(a)-(A)(e) above, each particular mechanism of inhibiting MIF biologic activity is distinct from the other because they proceed via materially different processes that require separate areas of search and consideration. For example, the species (A)(a) and (A)(b) requires search and consideration of the biological activity of distinct proteins (MIF or MIF receptor); species (A)(c) and (A)(d) require search and consideration of the alteration of gene expression of separate genes (those encoding MIF or MIF receptor, respectively); and species (A)(e) requires search and consideration of cellular and molecular control of MIF release.

In regard to the different species (B)(a)-(B)(g), each requires search and consideration of materially different agents that have separate and distinct effects and targets within an animal. For

example, species (B)(a)-(B)(c) utilize antibodies that bind to separate proteins, each protein having distinct biochemical and biological properties. Therefore, each species (B)(a)-(B)(c) requires separate search of each antibody target. Species (B)(d)-(B)(g) utilize distinct, non-antibody agents that would have been expected to have had separate effects within in host. Therefore, analysis of each of these species requires a search in the non-patent literature that is specific for each agent.

XI. Claim 78, drawn to recombinant cell lines, classified in Class 435, subclass 240.1.

XII. Claim 79, drawn to transgenic animals in which expression of MIF or its receptor is modified MIF, classified in Class 800, subclass 2.

The inventions are distinct, each from the other because of the following reasons:

The inventions of either of groups I and II are distinct from either of the inventions of groups III and IV because the former inventions are drawn to modulation of the MIF gene product (either at the level of gene expression or directly by modulation of protein activity) and the latter inventions are drawn to modulation of MIF receptor function. Therefore, examination of the former groups of inventions requires analysis of MIF protein whereas the latter groups of inventions require search and consideration of MIF receptors.

Each of the methods of groups I-IV, VI-X are distinct from the compositions of any of groups V, XI or XII, because none of said compositions are required for the practice of said methods and therefore, examination of said methods does not require search or consideration of any of said compositions *per se*.

The inventions of any of groups I-IV, VI, and VIII-X are distinct from the invention of group VII, because the latter invention is drawn to an *in vitro* assay which does not require search or consideration of any *in vivo* methods as required for the former groups of inventions. Considerations of *in vivo* methods requires analysis of, for example, means of administering compounds and delivering such to appropriate targets within a host.

The inventions of groups I-IV, and X, are distinct, one from the other, because they are drawn to materially different manners of inhibiting cytokine mediated toxicity. For example, the invention of groups I and III act directly at the level of gene expression and therefore requires search and consideration of means of modulating gene expression. In contrast, the invention of groups II and IV, are directed to means of modulating MIF protein or MIF receptor activity directly and therefore do not require search or consideration of gene expression. Further, the inventions act via distinct methods which require separate areas of search. For example, groups I and III, act via nucleic acid/nucleic acid interaction whereas groups II and IV act via protein/protein interaction. Each of the inventions of groups

I-IV are distinct from the invention of group X, because the latter invention utilizes combination therapies that require search and consideration of multiple interacting co-therapeutics. Further, the invention of group Xrequires search of antibodies such as anti-TNFα, which is not required for analysis of any of the inventions of groups I-IV.

Any of the inventions of groups I-IV are distinct from the invention of group VI because the former inventions are directed to inhibiting the function of the MIF or MIF receptor whereas the invention of group VI is drawn to modulating MIF release. Therefore, search of the invention of group VI does not require consideration of MIF or MIF receptor expression or activity.

Any of the inventions of groups I-IV, or VI are distinct from either the methods of groups VIII or IX because the latter inventions are directed to means of modifying the effects of steroids whereas the former inventions are directed to methods treating cytokine mediated toxicity. Therefore, the latter inventions require search and consideration of the metabolic effects of steroids and such analysis is not required for the inventions of groups I-IV or VI.

The inventions of groups V, XI, and XII, are distinct one from the other, because they are drawn to materially different compounds each of which requires separate areas of search and consideration. For example, analysis of the proteins of group V does not require consideration of recombinant gene expression as required for analysis of the invention of group XI or search of methods of genetically modifying multicellular organisms as required for the invention of group XII. Such latter considerations are not required for consideration of *in vitro* recombinant cell lines as defined by group XI.

The inventions of groups VIII and IX are distinct one from the other because they are drawn to materially different processes each of which requires separate areas of search and consideration. In the case of the invention of group VIII, means of inhibiting toxic side-effects of steroids are claimed. Therefore, search of such effects is required for analysis of this invention. In contrast, the latter invention is drawn to means of enhancing steroid action and therefore, search and consideration of steroid activity is required for examination of the latter invention.

The methods of groups VIII and IX are distinct from the invention of group X because the former inventions are drawn to modulation of steroid activity whereas the latter invention is drawn to the treatment of cytokine-mediated toxicity. Therefore, examination of the latter invention requires search and consideration of cytokine-mediated toxicity which is not required for analysis of means of modulating steroid activity.

Because these inventions are distinct for the reasons given above, have acquired a separate status in the art as shown by their divergent classifications and recognized divergent subject matter and

because the searches required for the separate inventions are not coextensive, restriction for examination purposes as indicated is proper.

Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian R. Stanton whose telephone number is (703) 308-2801. The examiner can normally be reached Monday-Thursday from 6:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jacqueline Stone, can be reached at (703) 308-3153. The fax phone number for this Group is (703) 308-4312.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Brian R. Stanton, Ph.D.
22 April 1996

BRIAN R. STANTON
PATENT EXAMINER
GROUP 1800